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10/595,585	09/14/2006	Beom-Seok Yang	300602005700	3070

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BEOM-SEOK YANG
JEONBO, APT 1202, 300-10
ICHON 1-DONG YONGSAN-GU
SEOUL,
KOREA, REPUBLIC OF

EXAMINER	
SWOPE, SHERIDAN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,585	YANG ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-15,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0906;0607*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election with traverse of Invention I and SEQ ID NO: 1 with a mutation at position 740, in their response of July 22, 2008, is acknowledged. The elected invention is directed to a method of making the polypeptide of SEQ ID NO: 1 with a mutation at position 740.

Applicants' traversal is based on the following argument. That all the claims share the common concept that increased autophosphorylation and tyrosine kinase activity can be induced in a protein which contains a DDR2 cytosolic tyrosine kinase domain by effecting certain mutations or increased phosphorylation at specific residues in the activation loop. This argument is not found to be persuasive for the following reasons. First, concepts of affecting activity by (i) creating mutations OR (ii) increasing phosphorylation, as agued by Applicants, cannot be a common concept because there is more than one concept. Second, as explained in the Restriction/Election requirement, the technical feature linking all claims appears to be that they all relate to DDR2, that DDR2 was well known in the art, and Ikeda et al, 2002 teach a method for making a DDR2 polypeptide having enhanced activity by coexpression with Src (Fig 3), which anticipates Claim 2. Thus, it is concluded that the claims share no special technical feature as defined by PCT Rule 13.2 because, as a whole, they do not define a contribution over the prior art. The lack of unity restriction is made FINAL.

With Applicants' response of July 22, 2008, Claim 22 has been cancelled and Claims 1-4, 6, 7, and 9-21 have been amended. Claims 1-21 are pending. Claims 1-15, 20, and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected

inventions, there being no allowable generic or linking claim. Claims 16-19 are hereby examined. It is noted that Claim 20 is encompassed by Group III.

Priority

The priority date granted for the instant invention is November 1, 2004, the filing date of PCT/KR04/02784, which disclosed the elected invention. If Applicants wish to obtain priority to KR 10-2003-0076967, an English language translation should be provided. In addition, it is noted that the subject matter of KR 10-2003-0076967 is an air-purifying hair dryer; thus, the Examiner questions whether Applicants' claim to foreign priority is to the wrong application.

Drawings

Figures 2-7, 11, and 14-16 are objected to for not being clearly described; the meaning of "CCB" is not explained. The figures or legends thereto should be amended.

Figures 5-10 are objected to for being informal; comprising paste-up lines.

Figure 8 is objected to for not being clearly described; the meaning of "Poly(D_4Y)n" is not explained. The figure or legend thereto should be amended.

Figure 12 is objected to for not being clearly described; the meaning of "p32-img" and "CCB" are not explained. The figure or legend thereto should be amended.

Abstract

The abstract is objected to because it is a single, run-on sentance.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Specification-Objections

The specification is objected to for failing to provide legends for Figures 8 and 9.

The specification is objected to for improper formatting. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claims-Objections

Claims 16-19 are objected to for reciting non-elected subject matter.

Claim 16 is objected to for the "and" on line 11, which should be moved to line 16.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claims 16, 17, and 19, the phrases "DDR2 cytosolic tyrosine kinase" and "DDR2 cytosolic tyrosine kinase domain" render the claims indefinite. Regarding "DDR2 cytosolic tyrosine kinase" the specification fails to define the structural or functional limitations of the kinases encompassed thereby. In addition, regarding "DDR2 cytosolic tyrosine kinase domain", the specification fails to define the structural limitations of any kinase domain of any "DDR2 cytosolic tyrosine kinase". The skilled artisan would not know the metes and bounds of the recited invention. Claims 17-19, as dependent from Claim 16, are indefinite for the same reason.

For Claim 16, the phrase "increased autophosphorylation or tyrosine kinase activity" renders the claim indefinite because it is unclear what the recited protein is compared to in order to determine if the activity is "increased". The skilled artisan would not know the metes and bounds of the recited invention. Claims 17-19, as dependent from Claim 16, are indefinite for the same reason. For purposes of examination, it is assumed that "increased autophosphorylation or tyrosine kinase activity" is assessed by comparing the mutated protein to the protein prior to any amino acid substitution.

For Claim 16, the phrase "sufficiently covering" renders the claim indefinite. The term "sufficiently" is a relative term which is not defined by the claim, the specification does not

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 17-19, as dependent from Claim 16, are indefinite for the same reason.

For Claim 16, the phrase "independently mutated" (line 7), in conjunction with "at least one tyrosine" (lines 3 & 6), renders the claim indefinite. It is unclear whether the claim means that, if more than one tyrosine is mutated, each mutation is technically performed using independent steps or the claim has some other meaning. The skilled artisan would not know the metes and bounds of the recited invention.

For Claim 19, the phrase "independently mutated" renders the claim indefinite for the same reason stated just above for claim 16.

For Claims 17 and 19, the phrase "of claim 16....the DDR2 cytosolic tyrosine kinase domain" renders the claim indefinite. It is unclear whether said phrase refers to the parent, non-mutated DDR2 cytosolic tyrosine kinase domain or the mutated DDR2 cytosolic tyrosine kinase domain. For Claim 19, the phrase "human DDR2 cytosolic tyrosine kinase domain" renders the claim indefinite for the same reason. The skilled artisan would not know the metes and bounds of the recited invention.

For Claim 17, the phrase "glutathione-S-transferase, thioredoxin or histidine oligomer" renders the claim indefinite. It is unclear whether said phrase encompasses (i) a glutathione-S-transferase tag, a thioredoxin tag, or a histidine oligomer tag, (ii) a glutathione-S-transferase oligomer tag, a thioredoxin oligomer tag, or a histidine oligomer tag, or (iii) a glutathione-S-transferase tag, a thioredoxin oligomer tag, or a histidine oligomer tag. The skilled artisan would not know the metes and bounds of the recited invention. If the meaning is meant to be (i) above,

it is suggested that the phrase be amended to "glutathione-S-transferase, thioredoxin, or histidine oligomer".

It is unclear whether Claim 19 encompasses only variants of SEQ ID NO: 1, variants of any "human DDR2 cytosolic tyrosine kinase domain", and/or variants of any variant of any "human DDR2 cytosolic tyrosine kinase domain". The skilled artisan would not know the metes and bounds of the recited invention. For purposes of examination, it is assumed that Claim 19 encompasses variants of any variant of any human protein having "DDR2 cytosolic tyrosine kinase activity".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the variant of SEQ ID NO: 1 consisting of a $Y^{740}F$ substitution, does not reasonably provide enablement for a method for making a variant of any protein having DDR2 kinase activity, wherein the variant has increased autophosphosphorylation and kinase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400

(Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 16-18 are so broad as to encompass any method for making a variant of any protein having DDR2 kinase activity, wherein the variant has increased autophosphosphorylation and kinase activity. Claim 19 is so broad as to encompass any method for making variants of any variant of any human protein having "DDR2 cytosolic tyrosine kinase activity", wherein the produced variant has increased autophosphosphorylation and kinase activity. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides to be made by the recited methods, as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to making the variant of SEQ ID NO: 1 consisting of a $Y^{740}F$ substitution.

While some methods for identifying proteins with kinase activity were known, it is not routine in the art to screen an essentially unlimited number of proteins for "DDR2 kinase" activity and then use a polynucleotide encoding said kinase to make any mutation in the "kinase domain" and then further test the encoded protein for increased autophosphorylation or kinase activity. Furthermore, the positions within a protein's sequence where amino acid modifications can occur with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 16-18, which encompasses all methods for making a variant of any protein having DDR2 kinase activity, wherein the variant has increased autophosphorylation or kinase activity. The specification does not support the broad scope of Claim 19, which encompasses all methods for making variants of any variant of any human protein having "DDR2 cytosolic tyrosine kinase activity", wherein the produced variant has increased autophosphorylation or kinase activity. The specification does not support the broad scope of Claims 16-19 because the specification does not establish: (A) the structural limitations/identity of all proteins having "DDR2" kinase activity; (B) regions of the protein structure which may be modified without affecting the desired "DDR2" kinase activity; (C) the general tolerance of the desired activity to modification and extent of such tolerance; (D) the structural limitations/identity of the kinase domain of all proteins having "DDR2" kinase activity; (E) which tyrosine residues in the kinase domain of all proteins having "DDR2" kinase

activity that may or may not be mutated in order to increase autophosphorylation or kinase activity; (F) a rational and predictable scheme for identifying all proteins having "DDR2" kinase activity; (G) a rational and predictable scheme for identifying all tyrosine residues of the kinase domain of all proteins having "DDR2" kinase activity that may or may not be mutated in order to increase autophosphorylation or kinase activity; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods for making any number of variants of any protein having DDR2 kinase activity, wherein the variant has increased autophosphosphorylation and kinase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of methods for making any number of variants of any protein having DDR2 kinase activity, wherein the variant has

increased autophosphosphorylation and kinase activity. The specification teaches only a single method of said genus, wherein four variants of a single DDR2 kinase protein are made. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for for making any number of variants of any protein having DDR2 kinase activity, wherein the variant has increased autophosphosphorylation and kinase activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al, 1986 in view of Karn et al, 1993. Ellis et al teach a method for making an insulin receptor variant consisting of a $Tyr^{1162}Phe$ mutation and that said variant has increased basal, insulin-independent receptor autophosphorylation and kinase activity (Fig 5). Ellis et al do not teach making a DD2 variant having a Tyr^{740} mutation, wherein the DD2 variant has increased basal autophosphorylation and kinase activity. Karn et al teach that Tyr^{740} of human DD2 kinase is analogous to Tyr^{1162} of the insulin receptor (Fig 2). It would have been obvious to a person of ordinary skill in the art to use recombinant methods, which were well-known, to prepare a

baculovirus encoding a DD2 protein consisting of mutation at Tyr^{740}, especially a $Tyr^{740}Phe$ substitution. Motivation to so derives from the desire to determine if, like insulin receptor activity, the Tyr^{740} residue of DD2 supports intramolecular, basal inhibition of DD2 activity. The expectation of success is high, as recombinant methods for making protein mutations, including use of baculovirus, addition of a tag, and use of insect host cells, were well-known in the art at the time of filing. Therefore, Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al, 1986 in view of Karn et al, 1993.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the reponse.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652